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Glomerular Filtration Rate and Supraphysiologic-Dose Anabolic-Androgenic Steroid Use: A Cross-Sectional Cohort Study

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Anabolic-androgenic steroids; chronic kidney disease; nephrotoxicity; testosterone

Millions of individuals worldwide have used supraphysiologic doses of anabolic-androgenic steroids (AAS) for athletics or personal appearance, but the effects of AAS on the kidney remained little studied.[1] In a recent cross-sectional cohort study evaluating cardiovascular function in 57 current AAS users, 28 past users, and 52 non-AAS-using weightlifters[2, 3], we obtained participants' standard chemistries, hematology, cystatin C, and endocrine measures (details in Item S1). With these data, we calculated participants' estimated glomerular filtration rate (eGFR), based on serum creatinine and cystatin C levels ($eGFR_{cr\text{-}cys}$), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[4] We conducted sensitivity analyses using CKD-EPI equations involving creatinine alone ($eGFR_{cr}$) and cystatin C alone ($eGFR_{cys}$).

Our primary outcome was the estimated mean difference in eGFR between AAS users and nonusers. Secondary outcomes, assessing potential effects of currency and duration of AAS

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use on eGFR, were 1) the estimated mean differences in eGFR among the subgroups of current AAS users, past AAS users, and nonusers; and 2) the association of eGFR with lifetime duration of AAS use. We estimated these associations using generalized linear regression models, adjusted for plausible confounding variables: age; race; lifetime history of any regular tobacco use; and lifetime history of abuse of or dependence on alcohol or illicit drugs (cannabis, opioids, stimulants, cocaine, ecstasy or polydrugs). We also performed exploratory analyses of possible mediators of the effect of AAS on eGFR (Item S2).

Users were demographically similar to nonusers (Table 1), but showed higher muscle mass, higher creatinine phosphokinase levels, decreased left ventricular ejection fraction, and decreased early left ventricular relaxation velocity. The $eGFR_{cr\text{-}cys}$, $eGFR_{cr}$, and $eGFR_{cys}$ were all lowest in current AAS users, intermediate in past users, and highest in nonusers (Table 2 and Figure S1). However, $eGFR_{cr\text{-}cys}$ was not significantly associated with duration of abstinence since last AAS exposure among former users (estimated mean increase [95% confidence interval] of 0.42 [−0.42, 1.26] mL/min/1.73m^2 per 1-unit increase in log-transformed months of abstinence; nominal $P = 0.32$), nor with lifetime duration of AAS use among users overall (estimated mean decrease of 0.5 [−0.3, 1.3] mL/min/1.73m^2 per additional year of AAS exposure; $P = 0.27$).

These findings may reflect 1) a direct toxic effect of AAS on the kidney; 2) an indirect effect caused by possible mediator variables, such as AAS-induced muscle breakdown or cardiovascular abnormalities; or 3) a non-AAS effect attributable to unmeasured confounding. The first hypothesis is consistent with one report of focal segmental glomerulosclerosis in ten long-term AAS users,[5] and reports associating AAS use with episodic acute kidney injury,[6, 7] which in turn increases the risk of progressive CKD.[8] The second hypothesis is tentatively supported by a mediation analysis (Item S2) suggesting a contributory role of AAS-induced cardiovascular dysfunction (provided these cardiovascular effects on eGFR are large relative to reciprocal effects of eGFR on cardiovascular function). The third hypothesis would posit unmeasured confounding variables, such as undetected drug exposures. Although we adjusted for participants' self-reported tobacco, alcohol, and illicit substance use, we lacked data on use of other potential nephrotoxins, such as non-steroidal anti-inflammatory drugs.

Several limitations to our study must be considered. First, we cannot exclude the possibility that the findings in our recruited sample of AAS users might not generalize to AAS users as a whole as a result of selection bias. Second, we cannot exclude unmeasured confounding, as just mentioned. Third, as with all studies employing retrospective assessments, there is a greater vulnerability to errors of classification (e.g., user status) and measurement (e.g., self-reported lifetime duration of AAS use and history of use of other substances). However, we used several strategies (urine testing, hair testing, and measurement of fat-free mass index, as detailed previously[2]) to assess whether participants were responding honestly. Furthermore, such errors of classification and measurement would likely bias the results towards the null, thus rendering our estimates of the association between AAS use and renal function more conservative. Fourth, because our original study was focused on cardiac function, we lacked measures of albuminuria, proteinuria, and more novel serum or urine

biomarkers of kidney injury, which offer additional information regarding CKD staging and prognosis. Fifth, we estimated glomerular filtration rate, rather than measuring it directly. Although the limitations of eGFR equations in AAS-using bodybuilders are unknown (and it is also unknown whether AAS affects cystatin C levels), the similarity of findings using all three CKD-EPI equations (Table 2), including those not using cystatin C, would seem to weigh against the possibility that the findings are artefactual.

While acknowledging these limitations, our findings may be clinically relevant, in that even mild reductions in kidney function are strongly associated with subsequent risk of chronic kidney disease,[9] which in turn is associated with higher all-cause mortality and cardiovascular disease events.[10] Thus, subsequent longitudinal studies of AAS and kidney function, assessing kidney biomarkers and possible structural damage, would be of value.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Long-Term Supraphysiologic-Dose AAS Users and Non-AAS-Using Weightlifters

	AAS Users			Non-Users	*P1* *	*P2**	*P3**	*P4**
Characteristics*	**All users (N = 85)**	**Current users (N=57)**	**Former users (N=28)**	**(N = 52)**				
Demographic features								
Age, y	42 (39–47)	42 (39–48)	42 (39–46)	43 (38–49)	0.98	0.78	0.59	0.55
Race†								
White	79 (93)	54 (95)	25 (89)	39 (69)				
Black	6 (7)	3 (5)	3 (11)	12 (23)	0.003	0.01	0.12	0.39
Asian	0	0	0	1 (2)				
Ethnic background†								
Not Hispanic	75 (88)	49 (86)	26 (93)	52 (96)	0.13	0.095	0.60	0.49
Hispanic	10 (12)	8 (14)	2 (7)	2 (4)				
Anthropomorphic measures								
Height, m	1.8 (1.7–1.8)	1.8 (1.7–1.8)	1.8 (1.7–1.8)	1.8 (1.7–1.8)	0.20	0.20	0.44	0.82
Weight, kg	97 (90–107)	95 (90–106)	98 (90–110)	91 (84–102)	0.026	0.043	0.087	0.61
Fat-free mass index‡	26 (24–28)	27 (25–29)	24 (25–28)	23 (21–25)	< 0.001	< 0.001	< 0.001	0.001
Exercise measures								
Age at onset of regular weightlifting, y	16 (14–20)	16 (15–22)	16 (14–19)	16 (15–21)	0.90	0.72	0.37	0.23
Lifetime duration of regular weightlifting, y	21 (15–26)	22 (16–27)	20 (14–26)	19 (11–28)	0.56	0.46	0.91	0.45
Time spent in aerobic exercise per week, min	90 (0–150)	88 (0–145)	95 (13–158)	65 (30–127.5)	0.40	0.62	0.27	0.51
Lifetime history of substance use								
Regular cigarette smoking§	27 (32)	17 (30)	10 (36)	19 (37)	0.58	0.54	1.0	0.63
Abuse of or dependence on alcohol or illicit drugs‖	44 (52)	25 (44)	19 (68)	19 (37)	0.11	0.56	0.01	0.042
AAS use								
Age at onset of AAS use, y	23 (19–30)	23 (19–31)	22 (19–26)	—	—	—	—	0.24
Cumulative lifetime total duration of AAS use, y	7.2 (3.9–11.4)	8.5 (4.0–12.5)	6.3 (3.7–10.0)	—	—	—	—	0.34
Cumulative lifetime dose of AAS, grams	363 (166–608)	370 (166–634)	343 (148–540)	—	—	—	—	0.46
Laboratory measures								

	AAS Users			Non-Users	*P1* *	*P2**	*P3**	*P4**
Characteristics*	**All users (N = 85)**	**Current users (N=57)**	**Former users (N=28)**	**(N = 52)**				
Blood urea nitrogen, mg/dL	18 (14–23)	19 (14–23)	17 (14–23)	16 (13–19)	0.015	0.014	0.14	0.53
Creatinine, mg/dL	1.1 (0.9–1.2)	1.1 (1.0–1.2)	1.0 (0.9–1.2)	0.9 (0.9–1.1)	0.001	< 0.001	0.26	0.095
Cystatin C, mg/L	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.8 (0.8–0.9)	0.8 (0.7–0.9)	< 0.001	<0.001	0.049	0.13
Creatine phosphokinase, mcg/L	570 (330–1030)	750 (510–1200)	320 (130–450)	280 (160–390)	< 0.001	< 0.001	0.9	<0.001
C-reactive protein, mg/L	1.7 (0.7–3.7)	1.7 (0.6–3.5)	1.8 (0.7–5.0)	1.9 (0.6–3.8)	0.95	0.78	0.75	0.56
Cardiovascular measures								
Hematocrit, %	49 (47–52)	50 (48–53)	47 (44–50)	45 (42–46)	< 0.001	< 0.001	0.004	0.001
Hemoglobin, g/dL	16 (15–17)	17 (16–18)	16 (15–17)	15 (15–16)	< 0.001	< 0.001	0.02	0.015
Average systolic blood pressure, mmHg	118 (108–128)	120 (110–128)	113 (108–123)	115 (108–123)	0.12	0.039	0.88	0.17
Left ventricular ejection fraction, %	49 (44–61)	47 (43–56)	60 (48–66)	62 (58–68)	< 0.001	< 0.001	0.12	<0.001
Diastolic tissue velocity, cm/sec	9.0 (8.0–11.0)	8.5 (7.4–10.6)	9.4 (8.9–12.1)	11.0 (9.8–12.7)	< 0.001	< 0.001	0.045	0.009

AAS = anabolic-androgenic steroids

*Data are reported as median (IQR) or n (%) as appropriate. *P* values were obtained from a Wilcoxon rank sum test or Fisher's exact test. P1 = all users versus nonusers; P2 = current users versus nonusers; P3 = past users versus nonusers; P4 = current users versus past users.

†Race and ethnic background were self-reported.

‡The fat-free mass index is calculated as: $(W(1\text{-}BF)/H^2) + 6.1(1.8\text{-}H)$, where W = weight in kilograms, H = height in meters, and BF = percent body fat.

§Any cigarette smoking beyond brief experimentation.

//Lifetime history of abuse of or dependence on alcohol, cannabis, opioids, stimulants, cocaine, ecstasy, or polydrugs by DSM-IV criteria.

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Table 2.

Estimated Glomerular Filtration Rate in AAS Users and in Non-AAS-Using Weightlifters

	AAS Users			Nonusers	Estimated Difference Between Groups*							
Variable	**All users**	**Current users**	**Past users**		**All Users vs. Nonusers**		**Current Users vs. Nonusers**		**Current Users vs. Past Users**		**Past Users vs. Nonusers**	
	(N = 85)	(N = 57)	(N = 28)	(N = 52)	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value
eGFR (mL/min/ 1.73 m²)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)								
Primary: creatinine- and cystatin-based	91.4 (19.8)	88.5 (20.6)	97.4 (16.9)	104.8 (14.3)	−14.1 (−20.3, −7.9)	<0.001	−17.0 (−23.7, −10.3)	<0.001	−9.1 (−16.6, −1.6)	0.018	−8.5 (−17.1, 0.1)	0.054
Secondary: creatinine-based	85.1 (19.6)	82.3 (19.7)	90.8 (18.3)	97.5 (14.4)	−12.9 (−19.0, −6.7)	<0.001	−15.0 (−21.4, −8.6)	<0.001	−6.3 (−14.9, 2.2)	0.145	−8.2 (−16.2, −0.2)	0.045
Secondary: cystatin-based	97.5 (21.8)	94.7 (23.3)	103.1 (17.6)	109.7 (15.7)	−13.3 (−20.3, −6.4)	<0.001	−16.7 (−24.4, −9.1)	<0.001	−10.0 (−0.3, −19.7)	0.043	−8.4 (−16.4, −0.3)	0.041
Category of eGFR (range in mL/min/ 1.73m²), by creatinine and cystatin	N (%)	N (%)	N (%)	N (%)	Risk Ratio† (95% CI)		Risk Ratio† (95% CI)		Risk Ratio† (95% CI)		Risk Ratio† (95% CI)	
≥ 90	44 (52)	25 (44)	19 (68)	41 (79)	3.1 (1.6, 6.0)	<0.001	3.6 (1.8, 7.0)	<0.001	1.8 (0.98, 3.3)	0.057	2.0 (0.86, 4.6)	0.11
60–89	38 (45)	29 (51)	9 (32)	11 (21)								
45–59	1 (1)	1 (2)	0	0								
30–44	0	0	0	0								
15–29	2 (2)	2 (4)	0	0								
<15	0	0	0	0								

eGFR = estimated glomerular filtration rate; AAS = anabolic-androgenic steroid.

*By generalized linear regression, adjusted for age, race, lifetime history of any regular tobacco use, and lifetime history of abuse of or dependence on one or more drugs of abuse

†Relative risk of eGFR < 90